

PHARMACEUTICAL COMPOSITIONS OF PAROXETINE

Field of the Invention

The present invention relates to stable pharmaceutical compositions of paroxetine and processes for their preparation.

Background of the Invention

The chemical name for paroxetine is (-) – trans-3- [(1, 3 – benzodioxol – 5 – yl oxy) methyl] – 4 – (4 – fluorophenyl) piperidine; (3S, 4R) – 3 – [5 – (1, 3 – dioxaindanyl) oxy methyl] – 4 – (p – fluorophenyl) piperidine, a 5 – hydroxy tryptamine (5 – HT, serotonin). Paroxetine functions as a re-uptake inhibitor and is disclosed in U.S. Patent No. 4,007,196. Paroxetine is indicated for the treatment of psychiatric problems including depression, Parkinson's disease, anxiety disorders, obsessive-compulsive disorders, panic disorders and post-traumatic stress disorder and other symptoms associated with excessive serotonin release. It is marketed in both immediate release and controlled release dosage forms by GlaxoSmithKline under the trade names of Paxil® and Paxil®CR respectively.

Solid dosage forms of paroxetine often develop certain physical instabilities, depending on the excipients used and the method of their preparation. This is evident by the development of a pink hue, softening of the dosage form or a decrease in the hardness upon storage. Skillful selection of pharmaceutically inert excipients and controlled manufacturing processes is necessary to obtain paroxetine dosage forms having the desired properties.

Few methods have been proposed or used to overcome these problems. For example, U.S. Patent No. 6,113,944 attributes the development of an undesirable pink hue on paroxetine tablets to water used during processing. The patent proposes overcoming this discoloration by preparing tablets using processes such as dry granulation and direct compression. These processes generally do not involve the use of water.

WO 03/057150 discloses that paroxetine tablets using hydroxypropyl methylcellulose (HPMC) and microcrystalline cellulose (MCC), two of the most widely accepted and used pharmaceutical excipients, lose their mechanical strength on storage. It is suggested that this problem of increased friability can be overcome by making paroxetine tablets which (i) are free of hydroxypropyl methylcellulose and (ii) include a filler that is non-hygroscopic or free of hydrochloric acid (HCl). In particular, it excludes the use of the widely accepted conventional filler, microcrystalline cellulose, and binder

hydroxypropyl methylcellulose. Hydroxypropyl methylcellulose is also used in dosage forms as a modified release polymer.

Thus there exists a need for the development of stable paroxetine dosage forms using conventional excipients without the discoloration and friability problems disclosed by the prior art. To that end, we have now developed an easy and simple process employing the wet granulation processing technique for preparing stable paroxetine compositions using conventional excipients.

Summary of the Invention

In one general aspect there is provided a pharmaceutical composition comprising paroxetine, microcrystalline cellulose, and one or more additional pharmaceutically acceptable inert excipients. The pharmaceutical composition is prepared by a wet granulation technique.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the paroxetine may be free paroxetine base and pharmaceutically acceptable salts, hydrates and solvates thereof. The pharmaceutically acceptable salt may be hydrochloride, maleate, acetate and mesylate.

The concentration of microcrystalline cellulose may be from about 15% to about 45% by weight. More particularly, the concentration of the microcrystalline cellulose may be about 30% by weight.

The pharmaceutically acceptable inert excipient may be one or more of fillers, binders, disintegrants, wetting agents, stabilizers, lubricants/glidants, flavoring agents and coloring agents.

The wet granulation may be carried out using one or more water miscible solvents, with or without water. The water miscible solvent may be lower alcohols and lower ketones. The lower alcohols may be one or both of ethanol and isopropyl alcohol. The water miscible solvent may be a mixture of water and isopropyl alcohol.

The pharmaceutical composition may be a tablet, capsule, caplet, spheroid, or granule. The pharmaceutical composition may further include a non-functional film-forming polymer coating.

In another general aspect there is provided a modified release pharmaceutical composition that includes paroxetine, microcrystalline cellulose, at least one modified

release polymer, and one or more pharmaceutically acceptable inert excipients. The pharmaceutical composition is prepared by wet granulation technique.

Embodiments of the modified release pharmaceutical composition may include one or more of the following features. For example, the modified release polymer may be one or more of cellulose derivatives, alginic acid derivatives, methacrylic acid derivatives, polysaccharides, and alkylene oxides. The modified release polymer may be hydroxypropyl methylcellulose of one or more of the low, medium and high viscosity grades of hydroxypropyl methylcellulose and mixtures thereof. The concentration of the hydroxypropyl methylcellulose may be from about 10% to about 30% by weight of the total composition weight.

The paroxetine may be free paroxetine base and pharmaceutically acceptable salts, hydrates and solvates thereof.

The concentration of microcrystalline cellulose may be from about 15% to about 45% by weight.

The one or more pharmaceutically acceptable inert excipients may be one or more of fillers, binders, disintegrants, wetting agents, stabilizers, lubricants/glidants, flavoring agents and coloring agents.

The wet granulation may be carried out using a water miscible solvent, with or without water. The water miscible solvent may be lower alcohols and lower ketones. The water miscible solvent may be a mixture of water and isopropyl alcohol.

The pharmaceutical composition may be a solid dosage form. The solid dosage form may be tablets, capsules, caplets, spheroids, and granules.

The pharmaceutical composition may further include an enteric polymer coating. The enteric polymer may be one or more of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methylcellulose acetate succinate, and one or more methacrylic acid copolymers. The enteric polymer coating may be about 1% to about 10% w/w of the total weight of the uncoated composition.

The pharmaceutical composition may further include a non functional film coating.

In another general aspect there is provided a process for the preparation of a pharmaceutical composition of paroxetine. The process includes (a) blending paroxetine,

microcrystalline cellulose, and one or more pharmaceutically acceptable excipients to form a blend; (b) wet granulating the blend to form granules; (c) drying and sizing the granules; and (d) lubricating and processing the granules into a solid dosage form.

5 Embodiments of the process may include one or more of the features described above.

10 In another general aspect there is provided a process for the preparation of a modified release pharmaceutical composition of paroxetine. The process includes (a) blending paroxetine with microcrystalline cellulose, hydroxypropyl methylcellulose, and one or more of fillers, binders and disintegrants to form a blend; (b) wet granulating the blend to form granules; (c) drying and sizing the granules; and (d) lubricating the granules and compressing into tablets.

15 Embodiments of the process may include one or more of the following features or those described above. For example, the process may further include (e) coating the tablet with enteric polymers up to a weight gain of about 10% w/w; and (f) film coating up to a weight gain of about 3% w/w.

20 In another general aspect there is provided a pharmaceutical composition including granules. The granules include paroxetine and microcrystalline cellulose. The granules are prepared by a wet granulation technique. Embodiments of the pharmaceutical composition may include one or more of the features described above.

25 In another general aspect there is provided a method of treating depression in a subject in need thereof. The method includes administering a pharmaceutical composition that includes paroxetine, microcrystalline cellulose, and one or more pharmaceutically acceptable inert excipients. The pharmaceutical composition is prepared by wet granulation technique.

30 Embodiments of the process may include one or more of the following features or those described above. For example, at least one of the pharmaceutically acceptable inert excipients may be hydroxypropyl methylcellulose and the pharmaceutical composition may be a modified release pharmaceutical composition.

35 The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims

Detailed Description of the Invention

Pharmaceutical compositions of paroxetine of the present invention may be prepared by the wet granulation technique using microcrystalline cellulose (MCC) as a filler, and hydroxypropyl methylcellulose (HPMC) as a modified release polymer without the development of either the pink hue or decrease in hardness upon storage.

Advantageously, the preparation of the granulation for tableting by the wet granulation process is amongst the oldest and most widely used techniques. Further, MCC, being a porous material, promotes easy wetting and rapid drying of wet granulation, and the granules exhibit good flow properties with a low lubricant demand.

The term 'stable' as used herein refers to mechanical stability of pharmaceutical composition of paroxetine wherein the composition does not lose its hardness or develop pink discoloration on storage at a temperature of 40°C and 75% relative humidity for 5 days.

The term 'paroxetine' as used herein includes paroxetine and pharmaceutically acceptable salts thereof, such as, hydrochloride, maleate, acetate, mesylate and hydrates and solvates thereof. In particular, paroxetine hydrochloride hemihydrate may be used.

The term 'pharmaceutical composition' as used herein refers to solid dosage forms for oral administration such as tablet, capsule, pill, spheroid, granule and the like. For example, tablets may be used.

The term "modified release dosage form" as used herein includes dosage forms intended for slow release, such as controlled release, prolonged release, delayed release, timed release, etc. that are capable of modifying the release of the drug up to a period of about 12 hours. For example, a delayed release dosage form may be used.

The term 'wet granulation' as used herein refers to granulation using water miscible solvent(s) with or without water. Suitable water miscible solvents include one or more of lower alcohols, such as ethanol and isopropyl alcohol (IPA), and lower ketones, such as acetone. For example, a mixture of water and IPA may be used.

MCC is purified partially de-polymerized alpha-cellulose. The de-polymerization is catalyzed by hydrochloric acid. MCC is a white, odorless, tasteless free flowing powder, which is insoluble in water, soluble in acids and most organic solvents and is practically insoluble in sodium hydroxide solution. The concentration of MCC may range from about 15% to about 45% by weight. In particular MCC at a concentration of about

30% may be used. It is commercially available under the trade name of Avicel® (manufactured by FMC Corporation) in various grades such as PH 103, PH 105, PH 101, PH 113 and PH 301. In particular, Avicel® PH 101 may be used.

Suitable modified release polymers include one or more of cellulose derivatives, alginic acid derivatives, methacrylic acid derivatives, polysaccharides, alkylene oxides and the like. Specific examples of cellulose derivatives include HPMC, hydroxypropyl cellulose (HPC), methylcellulose, carboxymethyl cellulose, and hydroxyethyl cellulose. Alginic acid derivative as used herein include alginic acid and its physiologically acceptable salts such as those of sodium, potassium, calcium, and the like. Examples of methacrylic acid derivatives include the various grades available under the trade name of Eudragit®. Examples of polysaccharides include chitosan, gellan, xanthan gum and the like. Examples of alkylene oxide include polyethylene oxide.

HPMC is cellulose ether, derived from alkali treated cellulose that is reacted with methyl chloride and propylene oxide. It has several names including 2-hydroxy propyl ether of methyl cellulose, propylene glycol ether of methyl cellulose, 2-hydroxy propyl methyl ether, hypromellose, etc. It is widely used as a modified release polymer, binder, and in coating compositions. It is commercially available as Methocel® (manufactured by Dow Chemicals) in various viscosity grades. The concentration of HPMC may range from about 10% to about 30% by weight. In particular, HPMC at a concentration of about 14% may be used. Examples of HPMC of low viscosity grades include Methocel E-5, Methocel E-15 LV, Methocel E-50 LV, Methocel K-100 LV and Methocel F-50 LV, whose 2% w/v aqueous solutions have viscosities of 5 cPs, 15 cPs, 100 cPs and 50 cPs, respectively. Examples of HPMC of medium viscosity grade include Methocel E4M and Methocel K4MCR, whose 2% w/v aqueous solutions have a viscosity of 4000 cPs. Examples of HPMC of high viscosity grade include Methocel K15M and Methocel K 100M whose 2% w/v aqueous solutions have viscosities of 15,000 and 10,000 cPs, respectively. For example, Methocel K4MCR and Methocel E-15 LV may be used.

Suitable pharmaceutically acceptable inert excipients include one or more of wetting agents, fillers, binders, disintegrants, coloring agents, flavoring agents, stabilizers, lubricants/glidants and plasticizers.

Suitable wetting agents used in the present embodiment include both ionic and non-ionic wetting agents. These include one or more of polyethylene glycols;

polyoxyethylene – polyoxypropylene block copolymers known as “poloxamer”;
polyglycerin fatty acid ester, such as decaglyceryl monolaurate and decaglyceryl
monomyristate, polyoxyethylene sorbitan fatty acid ester, such as polyoxyethylene
sorbitan monooleate, polyethylene glycol fatty acid ester, such as polyoxyethylene
5 monostearate, polyoxyethylene alkyl ether, such as polyoxyethylene lauryl ether;
polyoxyethylene castor oil and hardened castor oil, such as polyoxyethylene hardened
castor oil; sucrose ester of fatty acid, such as sucrose stearate ester and sucrose palmitate ester
and alkyl sulfate salt, such as sodium lauryl sulfate and magnesium lauryl sulfate; sodium
caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol
10 alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and other suitable wetting
agents. For example, poloxamer (available under the trade name of Lutrol) may be used.

Suitable fillers include one or more of calcium carbonate, calcium phosphate-
dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose powdered, dextrans,
dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch
15 pregelatinized, sucrose, sugar compressible, sugar confectioners, and other suitable fillers.

Suitable binders include one or more of polyvinyl pyrrolidone, methylcellulose,
hydroxypropyl cellulose, HPMC, gelatin, gum Arabic, ethyl cellulose, polyvinyl alcohol,
pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and
other suitable binders.

20 Suitable disintegrants include one or more of microcrystalline cellulose,
croscarmellose sodium, crospovidone, carboxymethyl starch sodium, sodium starch
glycollate, and other suitable disintegrants.

Suitable lubricants and glidants include one or more of colloidal anhydrous silica,
stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose
25 esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and the like.

Examples of plasticizers include one or more of polyethylene glycol, triethyl
citrate, triacetin, diethyl phthalate, dibutyl sebacate, and other suitable plasticizers.

Examples of stabilizers include one or more of antioxidants, buffers, acids, and
other suitable stabilizers.

30 Examples of coloring agents include any FDA approved colors for oral use.

In one process, the pharmaceutical composition of paroxetine may be prepared by a process which includes the steps of: blending paroxetine with microcrystalline cellulose, an additional filler, binder, and disintegrant; wet granulating the blend to form granules; drying the granules; lubricating the granules; and compressing the granules into tablets.

5 In another process, the modified release pharmaceutical composition of paroxetine may be prepared by a process which includes the steps of: blending paroxetine with microcrystalline cellulose, at least one modified release polymer, another filler, binder, and disintegrant; wet granulating the blend to form granules; drying the granules; lubricating the granules; and compressing the granules into tablets.

10 In yet another process, the modified release pharmaceutical composition of paroxetine may be prepared by a process that includes the steps of: blending paroxetine with microcrystalline cellulose, hydroxypropyl methylcellulose, another filler, binder, and disintegrant; wet granulating the blend to form granules; drying the granules; lubricating the granules; and compressing the granules into tablets.

15 The tablets prepared in any of the above embodiments may further be coated with one or more conventional film-forming polymers and / or modified release polymer. For example, the tablets may be coated with an enteric polymer to provide a delayed release of paroxetine.

Suitable film-forming polymers include one or more of ethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, hydroxyethyl cellulose; waxes, such as polyethylene glycol; methacrylic acid polymers, such as Eudragit[®] RL and RS; and the like. The coating may be performed using commercially available, ready-to-coat preparations, such as, various grades of Opadry[®].

25 Suitable enteric polymer include one or more of cellulose acetate phthalate, cellulose acetate, hydroxypropyl methylcellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methylcellulose acetate succinate; methacrylic acid copolymers, such as Eudragit[®] L 100-55, Eudragit[®] L 30, Eudragit[®] D55, Eudragit[®] L 100, Eudragit[®] S 100; and the like. The enteric coating may be continued up to a weight gain of about 1% to about 50% by weight of the uncoated tablet. In particular, the enteric coating may be continued up to a weight gain of about 1% to about 10% by weight of uncoated tablet and more particularly, up to a weight gain of about 5% to 10% of the uncoated tablet.

In one particular process, a modified release pharmaceutical composition of paroxetine may be prepared by a process which includes the steps of: blending paroxetine with microcrystalline cellulose, hydroxypropyl methylcellulose, lactose monohydrate, and polyvinyl pyrrolidone; wet granulating the blend to form granules, drying the granules, lubricating the granules; compressing into tablets; coating the tablets with enteric polymers up to a weight gain of 8-10% w/w, and coating with Opadry® up to a weight gain of 2-3% w/w.

The invention is further illustrated by the following examples, which is for illustrative purpose and should not be construed as limiting the scope of the invention in any way.

Examples 1 and 2

Ingredients	Amount (mg / tab)	
	Example 1	Example 2
Paroxetine hydrochloride hemihydrate	44.25	44.25
Hydroxypropyl methylcellulose (medium viscosity)	20.0	20.0
Hydroxypropyl methylcellulose (low viscosity)	5.0	5.0
Microcrystalline cellulose	50.0	50.0
Lactose monohydrate	40.0	55.0
Polyvinyl pyrrolidone	10.0	10.0
Water	qs	qs
Iso propyl alcohol	qs	qs
Magnesium stearate	3.0	3.0
Talc	2.75	2.75

Procedure:

For the preparation of tablets of paroxetine hydrochloride hemihydrate as per Examples 1 and 2, the drug was blended with other solid ingredients (except for the magnesium stearate and talc), granulated with a mixture of water and isopropyl alcohol (4:96 v/v), and dried. The dried granules were blended with magnesium stearate and talc and compressed into tablets. The compressed tablets were further enteric coated using an Eudragit® L-100-55 dispersion up to a weight gain of 8-10 % w/w and the enteric coated tablets then were further coated with Opadry up to a weight gain of 2-3% w/w.

The hardness and friability of the prepared tablets were tested immediately and after 15 days of storage at 40°C and 75% relative humidity using a Monsanto hardness tester and Roche's friabilator. The data is shown in Table 1.

Table 1. Hardness of Paroxetine hydrochloride hemihydrate tablets

Period	Hardness (Kp)		Friability (%)	
	Ex-1	Ex-2	Ex-1	Ex-2
Initial	9-11	9-11	0.45	0.02
After 15 days	9-11	9-11	0.38	0.06

The tablets of Examples 1 and 2 were tested for *in vitro* release of paroxetine hydrochloride hemihydrate in USP type II dissolution apparatus with #10 sinker at 100 rpm and temperature of $37 \pm 0.5^\circ\text{C}$, in 500 ml of 0.1N hydrochloric acid for 2 hours and then transferred to 900 ml of pH 6.8 buffer for the remaining period. 10 ml samples were withdrawn at pre-determined intervals and replaced with an equal volume of the appropriate pre-warmed dissolution medium. The withdrawn samples were analyzed for paroxetine hydrochloride hemihydrate content after appropriate dilution. The results of the study are shown in Table 2.

Table 2. *In vitro* release profile of paroxetine hydrochloride hemihydrate from the prepared tablets

Time (hours)	Cumulative percentage (%) of paroxetine hydrochloride hemihydrate released	
	Ex-1	Ex-2
2	0	1
3	5	5
4	12	11
5	22	19
6	30	30
8	51	54
10	68	77
12	81	93
14	90	101

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.